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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/807,114	LYAMICHEV ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed January 22, 2007. In view of the amendments to the claims and specification, the previous grounds of rejection and the objection to the title are withdrawn. This Office action contains new grounds of rejection necessitated by Applicant's amendments to the claims and is made FINAL.

2. Claims 66-72 are pending and have been examined herein.

New Grounds of Rejection

Claim Rejections - 35 USC § 112 – New Matter

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 66-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not appear to provide support for the amendment to the claims to recite a method for detecting an RNA having an accessible site sequence comprising the steps of, in addition to forming an extension product to identify an accessible site, further forming any 5' nuclease structure comprising any nucleic acid duplex comprising the accessible site, cleaving the cleavage structure with a 5' nuclease and detecting cleavage of the cleavage structure. The claims include

forming the cleavage structure prior to, after or simultaneously with the step of forming an extension product. The claims include the use of any 5' nuclease. Further, the claims include forming any cleavage structure comprising any nucleic acid duplex (DNA/DNA, DNA/RNA, RNA/RNA) that comprises the accessible site (e.g., any 6 nucleotides of the accessible site flanked by nucleotides of any identity or length that are distinct from that present in the RNA), and detecting cleavage of the cleavage structure by any means.

In the response filed January 22, 2007, Applicants point to pages 71, lines 9-12, and lines 19 to page 72 line 2; Figures 62-66, Example 19 and Example 15, and particularly page 194, lines 16-20 and Figure 47 as providing support for this amendment. However, the cited passages do not provide support for the full scope of the claimed method.

In particular, pages 71-72 of the specification define what constitutes a cleavage structure, a cleavage means and a cleavage agent and particularly state that a cleavage agent may be a 5' nuclease. However, the specification does not state the context of these teachings – i.e., the relationship between the cleavage agent or structure and a method for forming an extension product. Accordingly, these broad teachings regarding cleavage structures and agents do not provide support for the concept of a method for detecting an RNA having an accessible site sequence wherein the method comprises both the processes of forming an extension product to detect an accessible site sequence in an RNA and forming a 5' cleavage structure, cleaving the cleavage structure with a 5' nuclease and detecting cleavage of the cleavage structure.

Further, while Figures 62-66 exemplify cleavage structures, these figures do not provide support for the presently recited method. Additionally, Figure 47 provides the results of a sequencing assay, but also does not describe each of the method steps set forth in the present claims.

The specification (see Examples 18 and 19) teaches a method wherein accessible sites identified by the RT extension assay are used to design oligonucleotide probes for the INVADER assay. In particular, Example 19 provides support for the concept of a method wherein following the identification of an accessible site, probes are designed to be used in an INVADER assay, wherein the INVADER assay includes the steps of hybridizing the probe to an accessible site of an RNA (i.e., the probe is complementary to a region of a target nucleic acid that comprises the accessible site; see page 209 "All of the designs position the probe oligonucleotide directly in the accessible site"), and cleaving with CLEAVASE IX. However, these teachings do not provide support for each of the embodiments set forth in the present claims wherein following, prior to or occurring simultaneously with, a method for identifying an accessible site sequence in an RNA, the steps are performed wherein any cleavage structure is formed comprising any nucleic acid duplex (i.e., DNA/DNA, RNA/RNA, or DNA/RNA duplex) that includes an accessible site sequence (e.g., any 6 nucleotides of an accessible site flanked by nucleotides of any identity or length that are distinct from that present in the RNA), the cleavage structure is cleaved using any 5' nuclease, and cleavage of the cleavage structure is detected.

Additionally, the specification (page 42) teaches that:

> The present invention also provides a method, comprising: a) providing target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region comprising a double-stranded region; a bridging oligonucleotide capable of binding to said first and second non-contiguous single-stranded regions; a second oligonucleotide capable of binding to a portion of said first non-contiguous single-stranded region, and a cleavage means; b) mixing said target nucleic acid, said bridging oligonucleotide, said second oligonucleotide, and said cleavage means under conditions such that either said second oligonucleotide or said bridging oligonucleotide is cleaved.

However, this disclosure does not provide support for the presently claimed method wherein any nucleic acid is hybridized to a nucleic acid comprising an accessible site sequence to form a cleavage structure, the cleavage structure is cleaved with any 5' nuclease and the cleavage structure is detected prior to or following or occurring simultaneously with a method for detecting an RNA having an accessible site by performing a reverse transcriptase extension assay.

Claim Rejections - 35 USC § 112 second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 66-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 66-72 are indefinite over the recitation of "said extension product identifying an accessible site sequence of said RNA" because it is unclear as to how the extension product itself identifies an accessible site sequence (as opposed to the presence of an extension product indicating the presence of an accessible site sequence in the RNA).

Claims 66-72 are indefinite for failing to recite a clear nexus between the preamble of the claims and the final process step of the claims. The claims are drawn to a method for detecting an RNA having an accessible site sequence. However, the claims do not recite a step of detecting an RNA having an accessible site sequence. Rather, the claims recite a final step of detecting a cleavage structure. The claims also recite a step of forming an extension product, wherein the extension product identifies an accessible site sequence of an RNA. Thereby, it is unclear as to whether the claims are intended to be limited to a method for detecting an RNA having an accessible site sequence, a method for detecting an accessible site in an RNA molecule or a method for detecting cleavage of a cleavage structure. It is also unclear as to whether the RNA molecule recited, e.g., in claim 1, i) is the same as or distinct from the "RNA having an accessible site sequence" recited in the preamble and in step b) of claim 1. The claims should be amended to consistently refer to either RNA or RNA molecule or to state the relationship between the RNA and the RNA molecule.

Claims 66-72 are indefinite because it is unclear as to how the steps of forming a cleavage structure, cleaving the cleavage structure and detecting cleavage relate back to the remainder of the claim. Further, the claims do not recite a clear relationship between the nucleic acid duplex comprising the accessible site sequence and the RNA molecule. It is unclear as to whether the duplex that includes the accessible site sequence comprises the RNA sequence or includes only 6 to 10 nucleotides of an accessible site (i.e., the sequences to which the first region is complementary) flanked

by nucleotides of any number or identity or comprises any sequence from the RNA wherein the sequence also constitutes an accessible site.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 66-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over DesJardin (U.S. Patent No. 6,204,026).

DesJardin teaches a method comprising a) providing i) an SDA oligonucleotide primer comprising a first region complementary to an accessible site on an RNA sequence, and a second region that is located 5' of the first region and which is not complementary to the RNA sequence, ii) an RNA sequence comprising an accessible site, and iii) a reverse transcriptase; b) exposing the oligonucleotide primer and RNA

sequence to the reverse transcriptase under conditions in which the first region of the SDA oligonucleotide primer hybridizes to the RNA sequence and is extended to form an extension product; and c) detecting the primer extension product (col. 6, lines 3-9; and Table 1; col. 11-14). In particular, DesJardin teaches that the oligonucleotide primer comprises a 5' portion that consists of sequences that are not complementary to the target sequence, such as sequences that include a restriction enzyme site (col. 6, lines 3-9). The 3' portion of the oligonucleotide primer consists of a target specific sequence that is of a length of typically 10-25 nucleotides, but may contain fewer nucleotides (col 5, line 53 through col. 6, line 2). Thereby, DesJardin teaches the use of primers having a 3' first region of 10 or fewer nucleotides. Further, since the primer binds to the RNA and extends the RNA, the method of DesJardin is considered to be one wherein the presence of an extension product identifies an accessible site sequence of an RNA.

DesJardin (col. 6 line 52 through col. 7 line 6) teaches that any method may be used to detect the primer extension products. The reference (see e.g., Examples 6-8) exemplifies methods wherein the SDA extension products are detected using a hybridization probe. DesJardin does not specifically exemplify methods wherein the SDA primers are used in a reverse transcriptase assay to form an extension product and the extension product is detected by forming a 5' nuclease cleavage structure, cleaving the cleavage structure with a 5' nuclease and detecting the cleavage of the cleavage structure.

However, DesJardin (Example 10 and col. 2, lines 42-47) does teach a method wherein following an extension assay, the extension products are detected using a 5'

fluorogenic exonuclease assay. In particular, DesJardin exemplifies a method comprising performing RT-PCR, hybridizing a probe to the RT-PCR product to form a cleavage structure, cleaving the cleavage structure with a 5' nuclease and detecting cleavage of the cleavage structure.

Modification of the method of DesJardin so as to have performed the reverse transcription extension reaction using an SDA primer comprising a region complementary to an accessible site and a 5' non-complementary region, and then detecting the resulting extension products using a 5' fluorogenic nuclease assay would have resulted in a method comprising: a) providing an RNA with an accessible site, a reverse transcriptase and an oligonucleotide comprising a first region complementary to an accessible site on an RNA sequence, and a second region that is located 5' of the first region and which is not complementary to the RNA sequence; b) exposing the oligonucleotide primer and RNA sequence to the reverse transcriptase under conditions in which the first region of the oligonucleotide primer hybridizes to the RNA sequence and is extended to form an extension product; c) hybridizing a 5' fluorogenic probe to an extension product to form a 5' nuclease structure comprising a nucleic acid duplex comprising an accessible site sequence; d) cleaving the cleavage structure with a 5' nuclease; and e) detecting cleavage of said cleavage structure.

According, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of DesJardin so as to have detected the products of the SDA amplification reaction using a 5' nuclease cleavage

assay in order to have provided an equally effective means for detecting the SDA amplification products.

Regarding claims 67-71, DesJardin (col. 5 line 53 through col. 6 line 2) teaches that the target binding region of the primer is typically 10-25 nucleotides in length or may be fewer nucleotides. It is stated that the length of the primer is dependent on a number of factors including temperature, source of the primer, type of assay, and complexity of the target sequence. In view of the teachings of DesJardin that the 3' target binding region may be of a length of 10 or fewer nucleotides, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used SDA primers in the method of DesJardin which included a 3' target binding region of a length of 6-10 nucleotides in order to have provided an effective means for amplifying the target nucleic acid depending on the conditions under which the RT reaction was performed, on the sequence of the target nucleic acid and the optimum degree of specificity or non-specificity required for a particular assay.

Regarding claim 72, the 5' sequence of the primer of DesJardin is considered to have the property of being a sequence for "primer binding during further amplification of said extension product" since this 5' sequence could be used in a further primer extension assay as a binding site for the annealing of a primer.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER